Docket No. 0200-0004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Friedhoff et al.	Serial No.	09/704,554
Filed:	November 3, 2000	Art Unit:	1617
For:	Method of Treating Amyloid β Precursor Disorders	Examiner:	S. Jiang

#13 HKD 8-14-02

Commissioner of Patents and Trademarks

Washington, D.C. 20231

Please don't enter this declaration SJ 8/15/02

DECLARATION UNDER 37 C.F.R. 1.132

Dear Sir:

Dr. Edward Cullen declares as follows:

THAT, I have read the Office Action mailed March 27, 2002 in the above-identified application.

THAT, I received a Bachelor's degree in Chemistry in 1973 from Holy Cross College; thereafter, I received a Masters degree in Biological Chemistry from The University of Michigan in 1978; and in 1984 received a Doctorate in Biological Chemistry from The University of Michigan.

THAT, I have been employed, initially as a consultant from January 2000-March 2000, and subsequently as Executive Director, Project Management at assignee corporation, Andrx Corporation, in Ft. Lauderdale, Florida, since March 2000. Among my duties is to oversee the activities for the clinical applications of new formulations for lovastatin.

Prior to joining Andrx, I was employed by

EISAI INC., Teaneck, NJ from June 1991 January 2000
in the capacities of Associate Director, Preclinical Development; Director, Preclinical Research; Senior Director, Clinical Pharmacology

NEW YORK MEDICAL COLLEGE, Valhalla, New York from October 1988 to June 1991 Assistant Professor in the Department of Pharmacology.

THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, Baltimore, Maryland June 1984 to October 1988 Post-doctoral Fellow in the Department of Neuroscience

That I have authored or co-authored the following scientific publications:

Buxbaum, J.D., E.I. Cullen, and L.T. Friedhoff (2002) Pharmacological Concentrations of the HMG-CoA Reductase Inhibitor Lovastatin Decrease the Formation of the Alzheimer β-Amyloid Peptide *In Vitro* and in Patients. Frontiers in Bioscience 7, a50-59.

Friedhoff, L.T., E.I. Cullen, N.S.M. Geoghagen, and J.D. Buxbaum (2001) Treatment with Controlled-Release Lovastatin Decreases Serum Concentrations of Human β-Amyloid (Aβ) Peptide. Int. J. Neuropsychopharmacology, 4 (2):127 - 130.

Cullen, E.I., and R.E. Mains (1989) Post-translational processing of transfected mouse pro-Adrenocortico-trophin/endorphin in rat growth hormone-secreting tumor cells. Endocrinology 125, 1774-1782

May, V., E.I. Cullen, K.M. Braas, and B.A. Eipper (1988) Membrane-associated forms of peptidyl-glycine α-amidating monooxygenase activity in rat pituitary. J. Biol. Chem. 263, 7550-7554

Mains, R.E., V. May, E.I. Cullen, and B.A. Eipper (1988) Cellular mechanisms of peptide processing: focus on α-amidation. In: "Molecular Biology of Brain and Endocrine Peptidergic Systems" (K.W. McKerns and M. Chretien, eds.) pp. 201-213, Plenum Publishing, New York

Cullen, E.I., V. May, and B.A. Eipper (1987) Transport of ascorbic acid into pituitary cultures. Ann. N.Y. Acad. Sci. 493, 387-390

Cullen, E.I., and R.E. Mains (1987) Biosynthesis of amidated joining peptide from pro-ACTH/endorphin. Mol. Endocrinol. 1, 583-594

Mains, R.E., E.I. Cullen, V. May, and B.A. Eipper (1987) The role of secretory granules in peptide biosynthesis. Ann. N.Y. Acad. Sci. 493, 278-291

Eipper, B.A., V. May, E.I. Cullen, S.M. Sato, A.S.N. Murthy, and R.E. Mains (1987) Cotranslational and posttranslational processing in the production of bioactive peptides. In: "Psychopharmacology: The Third Generation of Progress" (H.Y. Meltzer, ed.) pp. 385-400, Raven Press, New York

Cullen, E.I., V. May, and B.A. Eipper (1986) Transport and stability of ascorbic acid in pituitary cultures. Mol. Cell. Endocrinol. 48, 239-250

Cullen, E.I., and F. Medzihradsky (1983) An artifactual component of drug-protein interaction generated *in vitro*. Life Sci. 33, 131-140

Medzihradsky, F., and E.I. Cullen (1982) Dynamic aspects of cell membrane structure. In: "Biological Transport of Radiotracers" (L.G. Colombetti, ed.) pp. 29-35, CRC Press, Boca Raton, Florida

Medzihradsky, F., E.I. Cullen, H.L. Lin, and G.G. Bole (1980) Drug sensitive ecto-ATPase in human leukocytes. Biochem. Pharmacol. 29, 2285-2290

Cullen, E.I., and F. Medzihradsky (1980) Concurrent isolation of granulocytes and lymphocytes with unaltered permeability, energy state, and metabolic capacity *in vitro*. Biochem. Med. 23, 133-143

WHEREFORE, having experience and expertise relevant to the art, I hereby declare as follows:

The subject invention concerns a method of lowering beta amyloid (Aβ) levels in a human by the administration of a controlled release dosage form containing an HMG CoA reductase inhibitor as an active ingredient.

The March 27, 2002 Office Action contends that the invention claimed in this application would have been obvious over the publication of Scolnick (WO/95/06470) in combination with Sabbaugh, et al. and May. However, a fair reading of Scolnick shows that the cited reference does not in any way teach or suggest lowering of the peptide, Aβ. By contrast, Scolnick describes that administering an HMG CoA reductase inhibitor lowers levels of a completely different protein, namely, Apolipoprotein isoform 4 (ApoE 4).

The Aβ peptide lowered by the method of the current invention, is completely different in structure, synthesis, and function from the ApoE 4 protein which Scolnick describes as essential to the treatment, prevention or amelioration of Alzheimer's Disease. However, this conclusion of Scolnick, that reduction of ApoE 4 is an effective method for treating Alzheimer's Disease, is completely incorrect based on current knowledge of lipid biochemistry and genetics, which has advanced tremendously since 1994 when the work of Scolnick was reported. ApoE 4 is a product of a variant gene, having reduced function, and is present in only a small percentage of the human population. Apolipoproteins are involved in the transport of lipids (fats) and cholesterol in the blood, the regulation of lipid and cholesterol levels in the body, and are components of lipoproteins, including chylomicrons, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low density lipoproteins (LDL), and high-density lipoproteins (HDL). It is now well known that reducing expression of a variant reduced-function gene product, such as ApoE 4, would not be expected to provide a beneficial therapeutic effect. Instead, reducing levels of an abnormal variant protein such as ApoE 4, would further reduce that function. Thus, if the reduced function of Apo E 4 played a crucial role in the pathology of Alzheimer's disease, reducing the levels of

this reduced function variant even further through treatment with an HMG Co-A reductase inhibitor would be expected to amplify the pathology and therefore increase the debilitating symptoms of Alzheimer's Disease.

This is in sharp contrast to the result of lowering Aβ levels, as in the claimed invention. In the claimed method of the subject invention, treatment with an HMG CoA reductase inhibitor was found to reduce Aβ levels. When present at elevated levels, Aβ can cause undesired plaque formation in the brain. Because Aβ is not a variant protein with reduced function (as is ApoE 4), but rather is a peptide which is harmful at elevated levels, reducing these levels can be useful in a variety of treatments and can be especially important in the prevention or treatment of Alzheimer's Disease.

In conclusion, it is my opinion that the method of lowering Aβ as described and claimed in the current application was unexpected and not an obvious result in view of the cited references or current knowledge in this area of medicine.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: 7-29-02

Edward Cullen

Edward Cullen PhD.